REMARKS

I. Status of the Claims. Upon entry of this Amendment, claims 14, 19, 20, 25, 55, 56, 72, 75, 77-80, 83-86 and 93-120 are pending. No claims have been amended. Claims 93-120 have been added. Support for the new claims is found throughout the specification, e.g., at paragraphs [0021], [0028], [0032], [0040, [0042], [0056], [0063], [0066], [0068], [0070], [0075], [0088], Example 1 (paragraphs [0102] and [0103]) and Fig. 2.

II. Examiners' Interview Summary. The Applicant and his representatives wish to thank Examiner Emch, Primary Examiner Kemmerer and SPE Stucker for the courtesies extended at the personal interview conducted at the Patent and Trademark Office on April 23, 2008. Attending the interview for Intellect Neurosciences were Dr. Daniel Chain (inventor of the present application), Applicant's representatives Mitchell Bernstein and Peter Ludwig, and Intellect's consultants, Dr. Kenneth Rock (Professor and Chairman, Department of Pathology, University of Massachusetts Medical Center) and Dr. Howard Federoff (Vice President of Health Sciences, Georgetown University).

During the interview, Dr. Chain recounted the history of the invention, describing how it had been conceived in conjunction with another project having to do with marine organisms. He pointed out that the invention involved administration of a free end specific antibody to bind amyloid β ("Aβ") in the cerebrospinal fluid. Dr. Rock summarized the substance of his Declaration that had been included with Applicant's previous response. He gave his view that provisional application 60/041,850 ("the provisional application") disclosed sufficient information to demonstrate to a person of ordinary skill in the art that Dr. Chain had been in possession of methods for treating Alzheimer's disease by contacting Aβ in the CSF of a patient with a free-end specific antibody (i.e., the pending claims). Dr. Rock reiterated the position set out in his Declaration, that Dr. Chain's invention was not limited to gene therapy. Dr. Federoff summarized the contents of his Declaration (also included with Applicant's previous response). He gave his view that the provisional application contained sufficient information to enable a person skilled in the art to practice the method called for in the pending claims.

The remainder of the interview was spent discussing the rejections set forth in the November 19, 2007 Office Action and, more specifically, whether the provisional application complied with the written description and enablement requirements set out in 35 U.S.C. §112, first paragraph and, thus, whether the pending claims are entitled to the priority date of the provisional application. No agreement was reached on these issues.

The Examiners made the following suggestions concerning topics the Applicant might wish to address in the instant Response:

(i) The ability of antibodies to cross the cross the blood brain barrier;

(ii) Application to the pending claims of new training materials on compliance with the written description requirement that were released by the Patent and Trademark Office April 11, 2008;

(iii) The meaning the first two paragraphs of the Summary of the Invention in relation to the written description requirement; and

(iv) Deficiencies in the Verma and Phillips references cited in the Nov. 19 Office Action.

The present Amendment is believed to address and incorporate the suggestions advanced by the Examiners at the interview.

III. Priority. The Examiner maintains that the instant application is not entitled to the priority date of provisional application 60/041,850, filed April 9, 1997 because the provisional application does not comply with the written description and enablement requirements set forth in 35 U.S.C. §112, first paragraph. The Examiner's position is not believed to be well taken and is traversed for the reasons set forth below.

(i) Enablement. The response filed on August 29, 2007 included a Declaration Under §1.132 from Dr. Federoff ("the first Federoff Declaration") setting forth his detailed analysis of the provisional application and his conclusion that the provisional application enabled one of ordinary skill in the art to practice the instant claims without undue experimentation. The Examiner responded by citing two references, Verma et al., *Nature* 369:239-242 (1997) ("Verma") and

Phillips, A.J., *J. Pharm. Pharmacol.* 53:1169-1174 (2001) ("Phillips"). The Examiner relied on these references to support the proposition that gene therapy was and continues to be unpredictable. The Examiner's position that the pending claims are not enabled by the provisional application is traversed on the grounds that the Examiner:

(a) failed to properly consider and address all relevant factors concerning enablement;

(b) failed to consider and address the evidence present in the first Federoff Declaration; and

(c) relied on references that are not applicable or relevant to the predictability of the claimed invention.

These grounds are discussed below in detail.

(a) The Examiner Failed to Consider Factors Relevant to Enablement

Factors to be considered for determining enablement include the breadth of the claims, the nature of the invention, the state of the prior art, the level of skill in the art, predictability/unpredictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *in re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). The MPEP states:

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole.

citing in re Wands, 858 F.2d at 737. Here, the Examiner's determination of non-enablement is erroneous because it relies only on only one of the Wand's factors while ignoring one or more of the other Wands factors.

The August 29, 2007 Response presented an analysis of the pending claims in view of each of the Wands factors and the first Federoff Declaration. Among the factors noted in the analysis were that the claims were narrowly drawn to treating a specific condition, i.e., accumulation of Aβ peptide in the brain and neurotoxicity of Aβ peptide in Alzheimer's disease, the advanced state of the prior art, the high level of skill in the art, the predictability of the invention based on, among other factors a rational, predictable basis for methods of using anti-Aβ antibodies for treating Alzheimer's disease, the high level of guidance provided in the provisional application for practicing the claimed invention, particularly gene therapy, the existence of prophetic examples and Dr. Federoff's conclusion that no further information beyond that provided by the provisional application would be required to enable one skilled in the art to practice the presently claimed invention.

In the Office Action, the Examiner agreed that the level of skill in the art is high and that gene therapy methods were practiced at the time of filing. The Examiner's sole reason for maintaining that the provisional application does not enable the pending claims is that gene therapy was and continues to be highly unpredictable with regard to therapeutic effects, as evidenced by the Verma and Phillips articles. Office Action at page 9. The Examiner, however, failed to consider and address the other Wands factors, particularly as articulated in Applicant's last response. Thus, the Examiner made no findings concerning the scope of the claims, predictability in view of well grounded rationale for using anti-Aβ antibodies for treating Alzheimer's disease, the prophetic examples, the high level of guidance in the application and Dr. Federoff's conclusion that no further information beyond that provided by the provisional application would be required to carry out the presently claimed invention. The Examiner's conclusion that the provisional application fails to enable the pending claims is thus erroneous and entirely inadequate because the Examiner failed to consider one or more of the Wands factors. *Id.* This conclusion is entitled to little weight in view of the analysis based on the first Federoff Declaration. This analysis evaluated and considered all of the Wands factors and established that the provisional application contains sufficient information to enable a person of ordinary skill in the art to practice the pending claims without undue experimentation. For these reasons standing alone, the Examiner's finding that the provisional application fails to enable the pending claims should be withdrawn.

(b) The Examiner Failed to Give Proper Weight to the Federoff Declaration

The finding that the provisional application fails to enable the pending claims should also be withdrawn because the Examiner failed to give proper weight to the first Federoff Declaration. In determining whether an applicant has overcome a rejection, the Examiner must consider Declarations under Rule 1.132. *In re Alton,* 76 F.3d 1168, 1176 (Fed. Cir. 1996) (Examiner's failure to "articulate adequate reasons to rebut [expert's] Declaration" is error as a matter of law for failure "to consider the totality of the record."), see also MPEP 2164.05 ("A declaration or affidavit is, itself, evidence that must be considered.") "The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." MPEP 2164.05.

As summarized immediately above, the first Federoff Declaration set forth a detailed analysis, including a direct consideration of many of the Wands factors. Based on this analysis, Dr. Federoff concluded that the provisional application enabled the pending claims. While the Examiner summarized the findings set forth in the first Federoff Declaration (*see* Office Action at pages 7-8), he failed to address any of Dr. Federoff's reasons for concluding the provisional application was enabled. With particular respect to predictability, the first Federoff Declaration stated that success of a gene therapy protocol could be predicted on four criteria: (i) An understanding of the disease mechanism; (ii) Selection of a therapeutic gene with action on a target component that is necessary for the pathogenesis of the disease; (iii) Selection of an appropriate virus vector that can deliver the therapeutic gene to the required anatomical area and express levels of the therapeutic gene sufficient to act on the target for the duration of the disease; and (iv) A means to deliver the therapeutic gene to the patient. *See* first Federoff Declaration at paragraph 12.

The first Federoff Declaration set out in detail how the disclosure of the provisional application satisfied each of these criteria for using gene therapy to practice the pending claims. The Examiner failed to make any finding concerning Dr. Federoff's finding on the predictability of gene therapy in general or the predictability of the application of gene therapy to the instant claims. Rather than address Dr. Federoff's findings, the Examiner relied on Verma and Phillips and arrived at the conclusion that gene therapy was and continues to be unpredictable. However, as stated in the second Federoff Declaration, the teachings in Verma and Phillips are general in nature and do not rebut the points in the first Federoff Declaration. Second Federoff Declaration at paragraphs 5-8.

Thus, the citation of Verma and Phillips is an inadequate response to Dr. Federoff's analysis concerning the predictability of gene therapy as applied to the instant claims. Moreover, the Examiner fails to make any attempt to address the other points raised in the first Federoff Declaration.

In summary, the Examiner erred by failing to respond to the points raised in the first Federoff Declaration. For this reason, additionally, the Examiner's finding that the provisional application fails to enable the pending claims should be withdrawn.

(c) Verma and Phillips Do Not Provide Evidence that the Provisional Application Fails to Enable the Pending Claims

A Second Declaration from Dr. Federoff accompanies this Amendment ("the Second Federoff Declaration"). In the Second Federoff Declaration, Dr. Federoff (an expert in the field of gene therapy, who was working in the field at the time the provisional application was filed) points out that the Examiner's reliance on Verma and Phillps is based on statements concerning clinical results that "provide no reason to doubt" that the provisional application enables the pending claims. Second Federoff Declaration at paragraphs 5 and 7. The Second Federoff Declaration further sets forth Dr. Federoff's reasons for concluding that the respective discussions in Verma and Phillips concerning potential drawbacks in using AAV for gene therapy are not well taken. Second Federoff Declaration at paragraphs 6 and 7. Based on these reasons, the Second Federoff Declaration concludes that it would be incorrect to draw an inference from either of Verma or Phillips that it would have been unpredictable as to whether AAV could be used to practice the instant claims. Second Federoff Declaration at paragraphs 6 and 7. Dr. Federoff concludes, "it is my opinion that the provisional application provided sufficient information to enable one of ordinary skill in the art to use gene therapy in April 1997 to inhibit accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the CSF of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ, as called for in the claims pending in the subject patent application." Second Federoff Declaration at paragraph 8. Thus, Dr. Federoff concludes that neither Verma nor Phillips establish that it would have required undue experimentation to practice the instant claims or that results of gene therapy were unpredictable. For this reason, additionally, the Examiner's finding that the provisional application fails to enable the pending claims should be withdrawn.

At the April 23 interview, Examiner Emch indicated he would give full consideration to a supplemental Declaration from Dr. Federoff explaining why, in Dr. Federoff's opinion, neither Verma nor Phillips raise any doubts that the provisional application enables the pending claims. Accordingly, the Examiner is respectfully requested to give favorable consideration to the accompanying Second Federoff Declaration.

(ii) Written Description. The response filed on August 29, 2007 included a Declaration Under §1.132 from Dr. Rock ("the first Rock Declaration") setting forth his point by point analysis of the provisional application and his conclusion that it disclosed sufficient information to establish that when it was filed the inventor had possession of the claimed methods for treating Alzheimer's disease by contacting Aβ in the CSF of a patient with an free-end specific antibody. In the Office Action, the Examiner maintained his position that the provisional application does not provide adequate written description for the pending claims, on the grounds that the provisional application "only contemplates" methods of gene therapy. The Examiner's position is not believed to be well taken and is respectfully traversed on the grounds that:

(a) the Examiner concedes that the provisional application describes the claimed invention and implicitly acknowledges the claims do not overreach the disclosure of the provisional application;

(b) the Examiner failed to give proper weight to the evidence present in the first Rock Declaration;

(c) the Examiner failed to apply the proper standard for finding the invention is related to a particular disclosed embodiment;

(d) the provisional application does not unambiguously limit the invention to gene therapy; and

(e) application of the new PTO training materials on written description leads to the conclusion that the provisional application satisfies the written description requirement.

(a) The Examiner Concedes that the Provisional Application Describes the Claimed Invention and Implicitly Acknowledges that the Claims Do Not Overreach the Disclosure of the Provisional Application

"[T]he test to determine if an application is to receive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application." *Noelle v. Lederman,* 355 F.3d 1343, 1348 (Fed. Cir. 2004); *see also Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000); *University of Rochester v. G. D. Searle & Co.,* 358 F.3d 916, 922 (Fed. Cir. 2004) ("The 'written description' requirement serves a teaching function, as a 'quid pro quo' in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'"), *citing Enzo Biochem, Inc. v. Gen-Probe Inc.,* 323 F.3d 956, 970 (Fed. Cir. 2002). The provisional application provides written description for the instant claims because one of ordinary skill in the art would recognize (1) the applicant was in possession of the claimed subject matter when the provisional application was filed and (2) the claims do not overreach the scope of the applicant's contribution to field, as disclosed in the provisional application.

With respect to the "possession test," the Office Action sets forth that, "The examiner agrees that the provisional application describes the claimed methods for inhibiting accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ." Office Action at page 5 (emphasis added). The Examiner thus concedes that inventor had "possession" of the presently claimed invention when the provisional application was filed. Here the possession test is satisfied because each feature of the claim is full supported in the specification.

With respect to ensuring the applicant does not overreach his disclosed contribution, as explained in the first Rock Declaration, one of ordinary skill in the art:

> [W]ould have recognized immediately that the inventor was in possession of a method of inhibiting the accumulation of Aβ or inhibiting the neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's disease with a free end specific antibody.

First Rock Declaration at paragraph 12. Dr. Rock stated explicitly that the provisional application:

> [W] ould have clearly conveyed to one of ordinary skill in the art that the therapeutic potential lies in the activity and effect of the end-specific antibodies, not by the means by which such antibodies are administered.

First Rock Declaration at paragraph 14. Dr. Rock further stated that:

> I would have immediately appreciated that treatment of Alzheimer's disease by contacting soluble Aβ in the CSF with a free end-specific antibody could be effected by directly administering such antibodies to a patient.

First Rock Declaration at paragraph 15.

In short, Dr. Rock (who works with and supervises those of ordinary skill in the art) concluded that upon reading the provisional application one of ordinary skill in the art would immediately appreciate that disclosed invention lay in providing free-end specific antibodies to Aβ to the CSF of Alzheimer's disease, where it would contact and bind Aβ. The Office Action states, moreover, "The Examiner also agrees that the skilled artisan would know that gene therapy was only one of a number of approaches to antibody treatment." The Examiner thus tacitly acknowledges that upon reading the provisional application one of ordinary skill in the art would appreciate that the disclosed invention lay in providing free-end specific antibodies to Aβ to the CSF of a patient with Alzheimer's disease, where it would contact and bind Aβ. Thus, as set forth in the first Rock Declaration and as tacitly acknowledged by the Examiner, the scope of the instant claims corresponds to the scope of the provisional application's contribution to methods of treating Alzheimer's disease. Because the scope of the present claims corresponds to the scope of the disclosure in the provisional application, the instant claims do not overreach applicant's contribution to the field as disclosed in the provisional application.

In summary, the invention defined by the pending claims is described in the provisional application and these claims do not overreach what the inventor has contributed to the field of art as described in the provisional application. The instant claims thus satisfy the written description requirement.

(b) The Examiner Failed to Give Proper Weight to the first Rock Declaration

The finding that the provisional application fails to provide written description for the pending claims should be withdrawn because the Examiner failed to give proper weight to the first Rock Declaration. In determining whether an applicant has overcome a rejection, the Examiner must consider Declarations under Rule 1.132. *In re Alton,* 76 F.3d 1168, 1176 (Fed. Cir. 1996) (Examiner's failure to "articulate adequate reasons to rebut [expert's] Declaration" is error as a matter of law for failure "to consider the totality of the record."), *see also* MPEP 2164.05 ("A declaration or affidavit is, itself, evidence that must be considered.") (emphasis in original) "The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." MPEP 2164.05 (emphasis in original).

The first Rock Declaration provides a detailed analysis to support the declarant's conclusion that the provisional application disclosed sufficient information to demonstrate to a person of ordinary skill in the art that the inventor had been in possession of methods for treating Alzheimer's disease by contacting Aβ in the CSF of a patient with a free end-specific antibody (i.e., the pending claims) and that the invention was not limited to gene therapy.

Among the reasons reported by Dr. Rock for arriving at this conclusion were that the provisional application:

(a) demonstrates that the inventor had possession of a free end-specific antibody, per se, and their usefulness in counteracting toxic effects of Aβ (First Rock Declaration at paragraph 10);

(b) discloses that a "therapeutic approach" to treating Alzheimer's disease is to inhibit or retard Aβ aggregation in the CSF (First Rock Declaration at paragraph 11);

(c) repeatedly discloses that the purpose of expressing a free end-specific antibody to Aβ is to provide the antibody to the CSF, where it will contact soluble Aβ, preventing accumulation into plaques" (First Rock Declaration at paragraph 12); and

(d) that certain other statements in the provisional application indicated that the inventor had possession of methods of treating Alzheimer's disease "without reference to gene therapy" (First Rock Declaration at paragraph 13); and

(e) that the separate discussion in the specification concerning the use of animal models to establish to the therapeutic potential of free end-specific Aβ antibodies "clearly conveyed to one of ordinary skill in the art that the therapeutic potential lies in the activity and effect of the end-specific antibodies, not the means by which such antibodies are administered" (First Rock Declaration at paragraph 14); and finally

(f) that "upon reading the specification, one of ordinary skill in the art would have immediately appreciated that treatment of Alzheimer's disease by contacting soluble Aβ in the CSF with a free-end specific antibody could be effected by directly administering such antibodies to a patient" (First Rock Declaration at paragraph 15).

The present Office Action summarizes the findings in the first Rock Declaration (*see* Office Action at pages 7-8), but then addresses only a few of them in a cursory and conclusory manner. Thus, the Examiner contends that the provisional application "only contemplates" gene therapy, but fails to point to any portion of the disclosure or the file history to support the contention that the invention is so-limited. The Examiner further contends that "when read in context" certain portions of the provisional application (that Dr. Rock interprets as establishing that the invention relates to treating Alzheimer's disease without reference to gene therapy) are restricted to gene therapy methods and compositions. Here too, the Examiner fails to point out any portions of the provisional application or file history that provide any guidance on the "context" in which these statements should be interpreted.

Nor is it adequate for the Examiner to respond Dr. Rock's statement that one of ordinary skill in the art would have immediately known that antibodies could be delivered by a means other than gene therapy by simply asserting that this "does not relieve Applicants' burden of complying with the requirements of 35 U.S.C. §112, first paragraph." This assertion is simply not relevant. Nowhere in the first Rock Declaration or Applicant's prior response was it stated that Applicant was "relieved" of complying with the written description requirement. The recognition

that antibodies could be administered directly to a patient is relevant because the first Rock Declaration sets out the reasons one of ordinary skill in the art would understand that the provisional application is not restricted to gene therapy. It is well established that the specification is to be interpreted as it would be understood by one of ordinary skill in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987); *Capon v. Eshhar,* 418 F.3d 1349, 1357 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.") Dr. Rock's reasoned finding that on reviewing the provisional application the skilled artisan would immediately understand that antibodies could be administered to a patient without resort to gene therapy is relevant because it provides evidence that one of ordinary skill in the art would understand that the provisional application is not restricted to gene therapy.

Other than the points discussed above, the Examiner failed to address any other point raised in the first Federoff Declaration. The requirements for maintaining a rejection are clearly set out in the MPEP:

> When a rejection is maintained, any affidavits relevant to the 35 U.S.C. 112, para. 1, written description requirement, must be thoroughly analyzed and discussed in the next Office Action.

MPEP 2163.05, *citing In re Alton,* 76 F.3d at 1176. Here, the Examiner did not adhere to the requirement and failed to give proper consideration to the first Rock Declaration. For this reason, the Examiner's finding that the provisional application fails to provide written description for the pending claims should be withdrawn.

(c) The Examiner Failed to Apply the Proper Standard for Finding the Invention Is Limited to a Particular Disclosed Embodiment

The Examiner specifically acknowledges the instant claims are described in the provisional application (*see* Office Action at page 6), but nonetheless asserts that the provisional application fails to provide written description for the claims because it "only contemplates" the use of gene therapy, to the exclusion of other methods. The Examiner, however, fails cite any precedent for the proposition that the claims of an application are limited because the application "only contemplates" a particular embodiment. Neither Federal Circuit precedent nor recently-issued PTO

guidelines on written description support an "only contemplates" standard for limiting an invention. The Office Action affords no guidance on what is needed to satisfy the "contemplation" standard for satisfying the written description requirement. In fact, there is no such standard. The only standard recognized by the courts is the possession test. Application of Federal Circuit precedent and the recently-issued PTO guidelines on written description demonstrates that the possession test is satisfied and that the provisional application provides written description for the pending claims.

The Examiner appears to argue that the invention disclosed in the provisional application is limited to a particular embodiment. Federal Circuit precedent, however, sets a high bar for finding that an invention is limited to a particular embodiment disclosed in an application. *Cooper Cameron Corporation v Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317, 1322-23 (Fed. Cir. 2002) (Finding no "essential element" test and "inventor is entitled to claim his invention in more than one way"). In cases where the Federal Circuit has found the invention to be limited to a particular disclosed embodiment, the court has carefully applied a standard that the embodiment was the only possible embodiment disclosed by the inventor. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) ("console only possible location" for controls; any other location for controls is "outside the stated purpose of the invention"); *Tronzo v. BioMet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998) ("clear that the [parent specification] discloses only conical shaped cups and nothing broader"); *Johnson Worldwide Assoc. v. Zebco Corp.*, 175 F.3d 985, 993 (Fed. Cir. 1999) (Claim not invalid for lack of written description where it did not "unambiguously limit" meaning of claim term). A claim need not include every component set forth in the specification.

Here, each and every limitation of the pending claims is described in the provisional application. The provisional application therefore provides a complete written description for the pending claims.

(d) The Provisional Application Does Not Unambiguously Limit the Invention to Gene Therapy

There is nothing in the provisional application that would lead one of ordinary skill in the art to conclude that gene therapy was the only method by which free end-specific antibodies could contact Aβ in the CSF. The first Rock Declaration explicitly states that nothing in the provisional application teaches that gene therapy was the only method by which recombinant free

end-specific antibodies to Aβ could be provided to the CSF of Alzheimer's patients (first Rock Declaration at paragraph 14). The first Rock Declaration also states that it would have been immediately appreciated that treatment of Alzheimer's disease could be effected by direct administration of antibodies (first Rock Declaration at paragraph 15). Moreover, the Examiner stated explicitly, "The examiner also agrees that the skilled artisan would know that gene therapy was only one of a number of approaches for antibody treatment." Office Action at pages 6-7. There is thus no dispute that upon reading the provisional application one of ordinary skill in the art would not find that the only method for administering free end-specific antibodies is via gene therapy. The instant situation thus does not meet the criteria set forth by the Federal Circuit for limiting an invention to the embodiment disclosed in the specification.

> The provisional application, moreover, sets forth:
>
> While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the inventions following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth as follows in the scope of the appended claims.
>
> Provisional application at page 46 lines 17-26.
>
> The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein, in combination with the knowledge of one of ordinary skill in the art.

Provisional application at page 47, line 14 through page 48, line 3.

Thus, the provisional application states explicitly that the embodiments set forth therein are subject to adaptation and are not limiting.

It is noted that during the April 23 interview, the Examiners requested that the present response discuss the Summary of the Invention in the context of whether the provisional application is limited to gene therapy. Applicant responded that in considering the Summary of the Invention one of ordinary skill in the art would conclude that gene therapy is one method of practicing the invention. There is nothing in the Summary of the Invention, however, that restricts the invention to gene therapy. Thus, although certain objects of the invention refer to gene therapy, other objects of the invention refer to treating Alzheimer's disease without reference to gene therapy.

Thus, by way of example, a separate paragraph of the Summary of the Invention section of the provisional application at page 10, lines 10-13 sets forth:

> It is therefore an object of the invention to overcome the deficiencies in the prior art by providing a novel method for preventing or inhibiting the progression of Alzheimer's disease.

Provisional application at page 10, lines 10-13.

Another paragraph of the Summary of the Invention section of the provisional application sets forth:

> A further object of the invention is to provide a method for preventing or inhibiting the progression of Alzheimer's Disease by also inhibiting the interaction of amyloid-β peptides mediating amyloid-β induced neurotoxicity and inhibiting the amyloid-β induced complement activation and cytokine release involved in the inflammatory process associated with Alzheimer's Disease.

Provisional application at page 10, line 22 through page 11, line 2.

These paragraphs of the provisional application thus refer to treatments without reference to gene therapy. Moreover, Dr. Rock also notes that these paragraphs refer to treatment of Alzheimer's without reference to gene therapy. *See* first Rock Declaration at paragraph 13.

The Summary of the Invention of the provisional application further sets forth:

> The present invention also avoids the problems associated with the repeated administration of pharmacological agents that requires chronic penetration of the blood brain barrier.

Provisional application at page 10, lines 6-9. When understood in the context of the provisional application as a whole, this text is understood to refer to overcoming problems associated with the failure of small molecules to cross the blood brain barrier. The Description of the Background Art thus discusses prior attempts to inhibit or retard Aβ aggregation. Provisional application at page 6, line 8 through page 7, line 14. The provisional application then sets forth:

> The effectiveness of these compounds in vitro [sic: in vivo], however, is likely to be modest for a number of reasons, most notably the need for chronic penetration of the blood brain barrier.

Provisional application at page 7, lines 11-14. Thus, to the extent that the first paragraph of the Summary of the Invention may be directed to gene therapy, one of ordinary skill in the art would understand that expression of antibodies is one way to overcome the problem associated with the inability of small molecules to cross the blood brain barrier.

One of ordinary skill in the art would not interpret the first paragraph of the Summary of the Invention to mean that gene therapy is required to deliver antibodies across the blood brain barrier. The provisional application clearly distinguishes treatment with small molecules from treatment with antibodies. Thus, after discussing treating Alzheimer's disease with small molecules and concluding that their lack of selectivity and inability to cross the blood brain barrier presents an obstacle to such treatments, the provisional applications sets forth:

> As another means of inhibiting or retarding Aβ aggregation, WO 96/25435 discloses the potential for a monoclonal antibody, which is end-specific for the free C-terminus of the Aβ 1-42 peptide, but not for the Aβ 1-43 peptide, in preventing the aggregation of Aβ 1-42.

Provisional application at page 7, lines 15-19. Thus, antibody treatments are distinguished from small molecule treatments.

Moreover, at the time the provisional application was filed, it was known that antibodies crossed the blood brain barrier. In response to a request by the Examiners at the April 23 interview, submitted herewith is a Second Declaration of Dr. Kenneth Rock, in which Dr. Rock discusses articles from peer reviewed journals which establish that by April 1997, it was appreciated by those of ordinary skill in the art that antibodies crossed the blood brain barrier.

Accordingly, when taken in the context of the provisional application as a whole and the state of the art when the application was filed, one of ordinary skill in the art would understand that a reference to gene therapy avoiding "problems associated with the repeated administration of pharmacological agents that requires chronic penetration of the blood brain barrier" refers to problems associated with small molecules and not to problems associated with antibody penetration of the blood brain barrier. At the time the provisional application was filed, it was known in the art that antibodies crossed the blood barrier. There is thus no basis to interpret the Summary of the Invention as indicating that gene therapy is required to deliver free-end specific antibody to the CSF.

For this reason, additionally, the Examiner's finding that the provisional application fails to provide written description for the pending claims should be withdrawn.

(e) Application of the PTO's New Training Materials On Written Description Lead to the Conclusion that the Provisional Application Satisfies the Written Description Requirement

On March 25, 2008, the PTO issued updated patent examiner training materials on the written description requirement ("the new training materials," available at http://www.uspto.gov/web/menu/written.pdf). The new training materials are incorporated into the Manual for Patent Examining Procedure. *See* PTO announcement available at http://www.uspto.gov/main/pat_exm_trng.htm. Application of the new training materials to the present situation leads to the conclusion that the provisional application provides written description for the pending claims because the provisional application does not disclose that gene therapy is critical to the functioning of the invention.

The new training materials application of *Tronzo v. BioMet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998) reinforces the Federal Circuit's standard that an invention is only limited to a

particular embodiment under the written description requirement when the embodiment is "critical" to the functioning of the invention. Example 1 of the new training materials is based on *Tronzo v. Biomet*. Claim 1 of the example is drawn generically to an "acetabular cup" prosthesis. See new training materials at pages 3-8.

According to the fact pattern in Example 1A of the new training materials, the generic claim is presented in a CIP application. The parent application describes an acetabular cup prosthesis where the cup is trapezoid, a truncated cone, or of conical shape, each of which is a conical-shaped cup. The parent application "touts the criticality of a conical cup over all other shaped cups." The new training materials conclude that the parent application does not provide written description for the generic claim because it disclosed only conical shaped cups, that the conical shape was critical to cup function compared to other cups, and that there was nothing in the earlier-filed application that shapes other than conical are part of the disclosure. According to the new training materials, the parent application provided written description only for claims drawn to cups with a conical shape. New training materials at pages 3-4.

The fact pattern of example 1B of the new training materials is similar to example 1A, except that claim 1 is a newly presented claim and the application is not a CIP. Once again, the new training materials conclude that the specification lacks written description for a generic claim to an "acetabular cup" prosthesis where the specification described only a conical-shaped cup that is "critical" to the function of the invention. New training material at pages 5-6.

Example 1C of the new training materials is similar to Examples 1A and 1B except the shape of the conical cup is disclosed as being "preferred." New training materials at page 6. Example 1C states that the specification discloses that the shape of the cup must allow the prosthesis to function effectively as an artificial hip socket, but does not define which shapes will allow the prosthesis to do so. Once again, the specification discloses only conical-shaped cups. The specification further "emphasizes that a conical cup is preferred over all other shaped cups." New training materials at page 6. Notwithstanding that the specification discloses only conical cups and emphasizes that the conical cup is preferred over all other shaped cups, Example 1C finds that the specification provides written description for a claim drawn generically to an "acetabular cup"

prosthesis, i.e., in contrast to Examples 1A and 1B, the invention is not limited to conical-shaped cups. New training materials at page 7. The new training materials set forth on page 7:

> Although the application states that conical shaped cups are preferred, the specification does not indicate that a conical shape is critical to cup function compared with other cup shapes. Thus, the shape of the cup is not a critical feature. Accordingly, a person of ordinary skill in the art would view the applicant to have been in possession of the generic subject matter claimed based on the single species disclosed in the specification because the invention as claimed will function in its intended manner without the specific disclosed conical shape.

The comparison of Examples 1A and 1B to Example 1C thus illustrate that the written description requirement only requires inclusion of a particular feature or limitation in a claim where the feature or limitation is described by the applicant as "critical" to the functioning of the invention. Here there is no such description or limitation in the provisional application.

Appendix C of the new training materials ("Decision Tree Where Benefit Claimed") is addressed to the instant case as asserted by the Examiner. Thus, the instant claims claim the priority of an earlier filing date and the Examiner asserts that the claims are broader than the earlier disclosure and original claims because the limitation of gene therapy is missing from the claims.[1] The Decision Tree in Appendix C emphasizes that under these circumstances the written description requirement is satisfied unless the missing limitation is "described by applicant as being a critical feature of the claims as a whole."[2]

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[1] The claims are described as broader than the disclosure of the provisional application only for the purpose of this analysis. Applicant does not believe that the claims are broader than the disclosure of the provisional application. Applicant maintains that each limitation of the claims is described in the provisional application. The Examiner has acknowledged that provisional application describes the claimed invention.

[2] It is noted that, according to the Decision Tree set forth in Appendix C, even if gene therapy were a critical feature of the claim (which it is not), the written description would nonetheless be satisfied if there is "express, inherent or implicit support for the claim as a whole." As set forth in both the first Rock Declaration and the first Federoff Declaration, expression of a free end-specific antibody in the brain of an Alzheimer's disease patient leads to secretion of the antibody into the CSF where it contacts Aβ and inhibits aggregation or neurotoxicity of Aβ. Thus, even if the specification were to disclose that gene therapy is a critical feature (which the specification does not) it would still provide written description for the pending claims because inhibiting aggregation or neurotoxicity of Aβ by contacting a free end-specific antibody to Aβ in the brain of an Alzheimer's patient is implicitly and inherently disclosed in the practice of the gene therapy methods.

The provisional application satisfies the standard for written description as set forth in the new training materials because it does not disclose gene therapy as a "critical" element of the invention. As discussed more fully above, the first Rock Declaration states that nothing in the provisional teaches that gene therapy is the only method by which free end-specific antibodies to Aβ can be provided to the CSF of Alzheimer's patients (first Rock Declaration at paragraph 14) and that it would have been immediately appreciated that treatment of Alzheimer's disease could be effected by direct administration of antibodies (first Rock Declaration at paragraph 15). The Examiner also acknowledged that, "the skilled artisan would know that gene therapy was only one of a number of approaches for antibody treatment." Office Action at pages 6-7. Dr. Rock and the Examiner thus agree that gene therapy is not "critical" to practicing the invention disclosed in the application. In short, "the invention as claimed will function in its intended manner without the specific disclosed" means of delivering free end-specific antibody to the CSF. *See* new training materials, Example 1C at page 7. Moreover, the provisional explicitly admits to "adaptations" of the methods set out therein. Thus, gene therapy is not a "critical feature of the claim as a whole." According to the new training materials the claims thus satisfy the written description requirement.

For all of the reasons set forth above, the provisional application provides written description for the subsisting claims.

(iii) Conclusion. For the reasons set forth above the provisional application satisfies the written description and enablement requirements set forth in 35 U.S.C. §112, first paragraph when measured against the subsisting claims. The Examiner is respectfully requested to accord all of the subsisting claims the filing date of the provisional application.

IV. Claim Rejections. The claim rejections set forth in the Office Action are summarized and addressed as follows.

(iii) Rejections Under 35 U.S.C. § 112, second paragraph

Claims 14, 20, 77 and 83 are rejected as indefinite for allegedly being incomplete for omitting essential steps that amount to a gap between the steps. The Examiner asserts it is unclear how exogenous antibodies would be present in vivo and that it is thus unclear where the contacting step occurs. The rejection is respectfully traversed. The subject application includes extensive

guidance concerning how exogenous antibodies may be administered, e.g., by intravenous administration or by expression of antibody genes in the CNS. *See* specification at pages 11-13. The present application and the provisional application disclose that antibodies contact amyloid-β protein after being secreted into the CSF from neuronal cells or after they cross the blood brain barrier. Thus, contrary to the Examiner's assertions, the application sets forth how exogenous antibodies may be present in vivo and where the contacting step occurs (in the CSF).

For the foregoing reasons, the bases for the instant rejection have been addressed and overcome. Reconsideration of claims 14, 20, 77 and 83 and withdrawal of the rejection thereof under 35 U.S.C. §112, second paragraph is requested.

(ii) Rejections Under 35 U.S.C. §102.

(a) Claims 14, 19, 20, 25, 55, and 56 remain rejected as allegedly anticipated under section 102(b) by Bard et al., *Nature Med.* 6:916-919 (2000), as evidenced by Su et al., *J. Neurosci. Res.* 53:177-186 (1998) and Frenkel et al., *J. Neuroimmunol.* 88:85-90 (1998). As set forth above in section III, the pending claims are entitled to a priority date of April 9, 1997. Bard was published in August 2000, i.e., after the priority date of the amended claims. Accordingly, Bard is not prior art to the pending claims. Thus, the rejection over Bard should be withdrawn.

(b) Claims 14, 19, 20, 25, 55, 56, 72, 75, 77, 80, 83 and 86 remain rejected under section 102(e) as anticipated by Schenk, U.S. Patent No. 6,787,637. As set forth above in section III, the pending claims are entitled to a priority date of April 9, 1997. Schenk has an earliest claimed priority date of May 28,1999, i.e., after the priority date of the pending claims. Accordingly, Schenk is not prior art to the pending claims. Thus, the rejection over Schenk should be withdrawn.

(iii) Rejections Under 35 U.S.C. §103.

Claims 78, 79, 80 and 84 remain rejected as allegedly obvious over Schenk in view of Saido et al., *Neurosci. Lett.* 215:173-176 (1996) and Harigaya et al., *Biochem. Biophys. Res. Comm.* 276:422-427 (2000). For the reasons set forth immediately above, neither Schenk nor Harigaya is prior art to the pending claims. Thus, the obviousness rejection should be withdrawn.

V. New Claims. New claims 93-120 have been added. These claims embrace different aspects of the present invention. Support for these new claims is found throughout provisional application 60/041,850, filed April 9, 1997, e.g., at page 12, lines 17; page 14, line 27-page 15, line 5; page 16, lines 12-19; page 28, lines 12-14; page 28, lines 23-25; page 31, lines 1-6; page 31, lines 13-18; Fig. 2 and Fig. 3. The new claims are thus entitled to the filing date of the provisional application. The new claims are patentable for at least the reasons set forth above for the other subsisting claims.

VI. Conclusion. All of the pending claims were fully enabled and described in the provisional application as of its April 9, 1997 filing date. The provisional thus satisfies the strictures of the first paragraph of 35 U.S.C. §112. Accordingly, the pending claims are entitled to the April 9, 1997 filing date of the provisional application.

This application is believed to be in condition for allowance and such action is earnestly solicited. If the Examiner believes there are remaining issues that may be advanced by an Examiner's interview or by entry of an Examiner's Amendment, he is invited to contact Applicant's attorney.

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